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Multiple Endocrine Neoplasias in the Era of Translational Medicine

Abstract

Medicine is an ever changing art, continuously adjusting to the shifting principles of philosophy and constant discoveries of science; it was beautifully said by Hippocrates: "… medicine does not do the same thing at this moment and the next…" Unabated dissemination of information is the only way that patients are assured that physicians will continue to practice medicine that reflects contemporary science. In the field of Multiple Endocrine Neoplasias (MENs), this is at least in part accomplished by biennially held International Workshops. The articles led by this editorial are the second and last installment of a collection of state-of-the-art presentations given in the course of the ninth such workshop that was held in Bethesda, MD, June 19–22, 2004. In addition to serving as an introduction to the articles that were written by some of the leaders in the field, the text of the editorial review that follows also supports the notion that MENs are poised to lead translational research in endocrinology: these disorders have benefited remarkably from the discoveries of the human genome project and are at a unique position to take advantage of new modalities in basic and clinical science

Key words
Pituitary tumors · Adrenal medulla · Paraganglioma · Hyperparathyroidism and jaw tumor syndrome · Multiple endocrine neoplasia-type 1

Introduction

Although almost a century has passed since Erdheim's description of the case of an acromegalic patient with a pituitary adenoma and three enlarged parathyroid glands, the term *multiple endocrine neoplasia* (MEN) was introduced only relatively recently, in 1968 [1] (Wermer had suggested the term multiple endocrine adenoma in 1954). After many years on the fringes of endocrinology, the field of MEN – like so much else in medicine – experienced a sort of a revolution in the late 1980s made possible by two advances: The first was theoretical – the introduction of the concept of "positional cloning", the idea that one can identify genes for human disease without knowing anything, or only knowing very little, about their function, but by knowing their position in the genome. The second was technical – the method of polymerase chain reaction (PCR), which made DNA, the genome in essence, available to biomedical researchers and, more importantly, clinicians. Cancer medicine and genetics were the fields that benefited most from the first applications of the new genomic concepts and technologies in endocrinology. Almost two decades later, after the first successful applications of positional identification of the MEN2 locus on chromosome 10q, *menin* (the product of the MEN1 gene), *PTEN*, *PRKAR1A* (which was also a known gene on 17q, having been identified as the main regulator of protein kinase A signaling), and a number of other genes and pathways in developmental diseases affecting the pi-

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Bibliography
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tuitary, thyroid, parathyroid, adrenal and gonadal glands, and the pancreatic islets, MENs are at the forefront of the post-genomic medicine

During these last 20 years, the MEN conditions were not only clinically defined but also molecularly elucidated by a relatively small group of investigators world-wide. These clinical researchers and molecular biologists who have dedicated their careers in elucidating the pathophysiology of MENs and in discovering possible treatments for endocrine neoplasms have been meeting every two to three years for the last 18 years under the auspices of the "International Workshops for MENs". The ninth such meeting was held in Bethesda, Maryland, USA (MEN2004) on June 20 – 22, 2004), and was supported mainly by a number of institutes among the National Institutes of Health but also by organizations such as the Endocrine Society and others. The articles that follow constitute the second compendium of the proceedings from the MEN2004 meeting. The first such collection was recently published in the *Journal of Internal Medicine* [2 – 9]. While the latter articles reported updates on mainly clinical issues related to the MEN syndromes, the present series focuses on genetics and molecular pathways that are involved in tumorigenesis in the tissues affected by the MENs. Not only do these reviews present some of the most recent accomplishments in the understanding of the pathophysiology of MENs, they also demonstrate the influence of this field of medicine on contemporary translational research.

MENs: What is New?

We mentioned that the MEN field is already in the era of post-genomic medicine. Does that mean that all the genes that could be identified have been found? The answer is clearly "No". Traditional positional cloning may have left out several genes with a putative role in endocrine tumorigenesis that could not be identified due to the small number of families affected, non-Mendelian genetics in their inheritance patterns, or even sporadic occurrence. The first paper in our series by Daly et al. [10] identifies several kindreds with familial pituitary adenomas that do not harbor coding sequence mutations of the known pituitary tumor-related MEN genes (*GNAS*, *MEN1* and *PRKAR1A*). Although the known genes' participation in the pathogenesis of tumors in these families can not be excluded, the evidence is in support of additional genes that serve as primary, germline hits in pituitary oncogenesis. Families with MEN 1 that map to 11q13 [11] or Carney complex (CNC) that map to 17q22 or elsewhere [12] and kindreds with pituitary tumors [13,14] that do not have *MEN1* or *PRKAR1A* coding sequence mutations have been reported [15]. Investigators have also pointed to the existence of isolated familial acromegaly [13 – 15], which is likely to be genetically heterogeneous [16]. Advances in genetic mapping techniques such as the use of single-nucleotide polymorphism (SNP)-based arrays and related new software are expected to assist greatly in the identification of these new gene(s) or novel mutations in existing genes [11], which may or may not be part of known molecular pathways [15].

What are these pathways? The second article in our series refers to the involvement of the fibroblast growth factor (FGF) signaling in pituitary tumorigenesis [17]. Ezzat and his co-workers have previously identified pituitary tumor-derived fibroblast growth factor receptor 4 (ptd-FGFR4), an alternatively transcribed N-terminally truncated cytoplasmic receptor isoform. Unlike wild-type FGFR4, ptd-FGFR4 facilitates cell transformation and results in pituitary tumor formation in transgenic mice [18]. They have also shown the importance of this pathway in a number of other tumors, some of them endocrine [19,20]. The review in this issue [17] underscores what is true for almost all other endocrine tumor genes or pathways discovered in the MEN field: a molecular network that is so critical for cellular homeostasis may become tumorigenic due to genetic defects, mild perturbations of the signaling balance, or both. This is an important point because it may provide the explanation for why the MEN genes so frequently play a role in the etiopathogensis of sporadic tumors of the respective endocrine glands – although we can not yet extrapolate back to whether molecules such as the FGFs or their receptors will be found to have germline mutations in other forms of MENs.

What regulates these pathways? Transcriptional control over pituitary-expressed genes is mediated by a variety of factors; responsiveness to these molecules may be affected by the state of the target gene's sequence. Epigenetic changes in the pituitary transcriptome are slowly but steadily being recognized. W. E. Farrell elegantly reviews the status of the investigations in this field [21]. His group has published extensively on methylation-mediated changes of the expression of genes, such as GADD45-gamma, retinoblastoma, and p16, which have not been found as mutated in human pituitary tumors. These genes, however, are known to play an important role in both pituitary development and oncogenesis from animal model and other studies [22 – 24].

The papers by Hendy et al. [25] and Agarwal et al. [26] present yet another signaling pathway obviously important for endocrine tumorigenesis, that of the *menin* tumor suppressor. It has now been eight years since the identification of *MEN1*, the gene that is responsible for almost all cases of MEN1 [26], with few notable exceptions [11]. Interestingly, however, compiled germline and somatic mutations show almost no genotype/phenotype correlation. The *MEN1* gene codes for a 67 kDa protein that is widely present mainly in the nucleus of expressing cells. The reviews by Hendy et al., and Agarwal et al. present *MEN1*'s compelling story: a molecule for which nothing was known prior to its positional cloning, which now is at the center of a complicated interactive network that includes junD, NF-kB, PEM, COMPASS, SMAD3, RPA2, FANCD2, NM23beta, non-muscle myosin heavy chain II-A, GFAP, and/or vimentin. In addition, animal models, including menin-overexpressing fruit flies, reveal the many facets of this gene's function [27,28].

The last three articles in our current series present advances in areas related to the classic MEN syndromes. Wang et al. present an up-to-date review on the *HRPT2* gene [29]. *HRPT2* is mutated in the germline of patients with the hyperparathyroidism-jaw tumor syndrome and in the somatic state in a large number of parathyroid carcinomas [30,31]. Like the *MEN1* gene, there was no information on *HRPT2*'s molecular interactions prior to this gene's cloning; microarray studies have recently revealed a multitude of pathways that this gene may interact with in promoting parathyroid tumorigenesis [32].

Bertherat et al. discuss the advances in two distinct areas of endocrine neoplasias that constitute part of a number of inherited conditions [33]. *PRKAR1A*, the gene for CNC, is found mutated in a fifth of all sporadic adrenocortical adenomas [34], and one or the other succinate dehydrogenase (SDH) subunit (*SDHB*, *SDHC*, and *SDHD*), along with the other MEN genes, *RET* and *VHL*, are found to be mutated in almost a third of all pheochromocytomas and paragangliomas [35]. Some phenotype-genotype correlation has been found [36], but a lot remains to be done in that field, including cloning the genes responsible for other forms of hereditary paragangliomas [37]. The latter syndromes such as the Carney triad or the dyad of gastric stromal tumors and paragangliomas [37] are in the differential of the case reported in our last article of this special issue [38]. The co-occurrence of non-adrenal pheochromocytoma and an adrenocortical adenoma has been reported before in some patients with the Carney triad.

Summary

It was recently said that "progress in dissecting signaling pathways has begun to lay out a circuitry that will likely mimic electronic integrated circuits in complexity and finesse, where transistors are replaced by proteins (e.g. kinases and phosphatases) and the electrons by phosphates and lipids" [39]. Translational Medicine today identifies these complex interactions, making it no surprise that less than 30 000 (rather than 100 000 genes) are enough to produce a human phenotype; it is not the number of genes that is important, but rather the number and quality of synapses between them, as well as their post-translational changes. In post-genomic medicine, the field of MENs has given endocrinology a place at the frontiers of biomedical research. Endocrine concepts and the reemergence of signaling as the main way of understanding the complex interactions of genes that lead to endocrine tumors are essential for the current approach to cancer research and directing the development of new drugs that are tailored to genomic-translational information [40]. This is already happening in the MEN field with the development of inhibitors of RET tyrosine kinase activity that are in clinical trials on the footsteps of Gleevec and related "molecularly designed" drugs [41].

References

[1] Carney JA. Familial multiple endocrine neoplasia: the first 100 years. Am J Surg Pathol 2005; 29: 254 – 274
[2] Marx SJ, Stratakis CA. Multiple endocrine neoplasia – introduction. J Intern Med 2005; 257: 2 – 5
[3] Bilezikian JP, Brandi ML, Rubin M, Silverberg SJ. Primary hyperparathyroidism: New concepts in clinical, densitometric, and biochemical features. J Intern Med 2005; 257: 6 – 17
[4] Bradley KJ, Hobbs MR, Buley ID, Carpten JD, Cavaco BM, Fares JE, Laidler P, Manek S, Robbins CM, Salti IS, Thompson NW, Jackson CE, Thakker RV. Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour (HPT-JT) syndrome. J Intern Med 2005; 257: 18 – 26
[5] Carling T, Udelsman R. Parathyroid surgery in familial hyperparathyroid disorders. J Intern Med 2005; 257: 27 – 37
[6] Tonelli F, Gratini G, Falchetti A, Nesi G, Brandi ML. Surgery for gastroenteropancreatic tumours in multiple endocrine neoplasia type 1: review and personal experience. J Intern Med 2005; 257: 38 – 49
[7] Machens A, Ukkat J, Brauckhoff M, Gimm O, Dralle H. Advances in the management of hereditary medullary thyroid cancer. J Intern Med 2005; 257: 50 – 59
[8] Pacak K, Ilias I, Adams KT, Eisenhofer G. Biochemical diagnosis, localization, and management of pheochromocytoma: focus on multiple endocrine neoplasia type 2 in relation to other hereditary syndromes and sporadic forms of the tumour. J Intern Med 2005; 257: 60 – 68
[9] Lips CJ, Höppener JW, Van Nesselrooij BP, Van der Luijt RB. Counselling in multiple endocrine neoplasia syndromes: from individual experience to general guidelines. J Intern Med 2005; 257: 69 – 77
[10] Daly AF, Jaffrain-Rea M-L, Beckers A. Clinical and genetic features of familial pituitary adenomas. Horm Metab Res 2005; 37: 347 – 354
[11] Hao W, Skarulis MC, Simonds WF, Weinstein LS, Agarwal SK, Mateo C, James-Newton L, Hobbs GR, Gibril F, Jensen RT, Marx SJ. Multiple endocrine neoplasia type 1 variant with frequent prolactinoma and rare gastrinoma. J Clin Endocrinol Metab 2004; 89: 3776 – 3784
[12] Kirschner LS, Sandrini F, Monbo J, Lin JP, Carney JA, Stratakis CA. Genetic heterogeneity and spectrum of mutations of the PRKAR1A gene in patients with the carney complex. Hum Mol Genet 2000; 9: 3037 – 3046
[13] Soares BS, Frohman LA. Isolated familial somatotropinoma. Pituitary 2004; 7: 95 – 101
[14] De Menis E, Prezant TR. Isolated familial somatotropinomas: clinical features and analysis of the MEN1 gene. Pituitary 2002; 5: 11 – 15
[15] Jorge BH, Agarwal SK, Lando VS, Salvatori R, Barbero RR, Abelin N, Levine MA, Marx SJ, Toledo SP. Study of the multiple endocrine neoplasia type 1, growth hormone-releasing hormone receptor, Gs alpha, and Gi2 alpha genes in isolated familial acromegaly. J Clin Endocrinol Metab 2001; 86: 542 – 544
[16] Stratakis CA, Kirschner LS. Isolated familial somatotropinomas: does the disease map to 11q13 or to 2p16? J Clin Endocrinol Metab 2000; 85: 4920 – 4921
[17] Ezzat S, Asa SL. FGF receptor signaling at the crossroads of endocrine homeostasis and tumorigenesis. Horm Metab Res 2005; 37: 355 – 360
[18] Ezzat S, Zheng L, Asa SL. Pituitary tumor-derived fibroblast growth factor receptor 4 isoform disrupts neural cell-adhesion molecule/N-cadherin signaling to diminish cell adhesiveness: a mechanism underlying pituitary neoplasia. Mol Endocrinol 2004; 18: 2543 – 2552
[19] Ezzat S, Huang P, Dackiw A, Asa SL. Dual inhibition of RET and FGFR4 restrains medullary thyroid cancer cell growth. Clin Cancer Res 2005; 11: 1336 – 1341
[20] St Bernard R, Zheng L, Liu W, Winer D, Asa SL, Ezzat S. Fibroblast growth factor receptors as molecular targets in thyroid carcinoma. Endocrinology 2005; 146: 1145 – 1153
[21] Farrell WE. Epigenetic mechanisms of tumorigenesis. Horm Metab Res 2005; 37: 361 – 368
[22] Farrell WE, Clayton RN. Epigenetic change in pituitary tumorigenesis. Endocr Relat Cancer 2003; 10: 323 – 330
[23] Bahar A, Bicknell JE, Simpson DJ, Clayton RN, Farrell WE. Loss of expression of the growth inhibitory gene GADD45gamma, in human pituitary adenomas, is associated with CpG island methylation. Oncogene 2004; 23: 936 – 944
[24] Simpson DJ, McNicol AM, Murray DC, Bahar A, Turner HE, Wass JA, Esiri MM, Clayton RN, Farrell WE. Molecular pathology shows p16 methylation in nonadenomatous pituitaries from patients with Cushing's disease. Clin Cancer Res 2004; 10: 1780 – 1788
[25] Hendy GN, Kaji H, Sowa H, Lebrun J-J, Canaff L. Menin and the TGF-β superfamily member signaling via the Smad pathway in pituitary, parathyroid, and osetoblast. Horm Metab Res 2005; 37: 375 – 379
[26] Agarwal SK, Kennedy PA, Scacheri PC, Novotny EA, Hickman AB, Cerrato A, Rice TS, Moore JB, Rao S, Ji Y, Mateo C, Libutti SK, Oliver B, Chandrasekharappa SC, Burns AL, Collins FS, Spiegel AM, Marx SJ. Menin molecular interactions: insights into normal functions and tumorigenesis. Horm Metab Res 2005; 37: 369 – 374
[27] Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. Nat Rev Cancer 2005; 5: 367 – 375
[28] Hughes CM, Rozenblatt-Rosen O, Milne TA, Copeland TD, Levine SS, Lee JC, Hayes DN, Shanmugam KS, Bhattacharjee A, Biondi CA, Kay GF, Hayward NK, Hess JL, Meyerson M. Menin associates with a trithorax family histone methyltransferase complex and with the hoxc8 locus. Mol Cell 2004; 13: 587 – 597
[29] Wang PF, Tan M-H, Zhang C, Marsh D, Morreau H, Teh BT. HRPT2, a tumor suppressor gene for hyperparathyroidism-jaw tumor syndrome. Horm Metab Res 2005; 37: 380 – 383

[30] Shattuck TM, Valimaki S, Obara T, Gaz RD, Clark OH, Shoback D, Wierman ME, Tojo K, Robbins CM, Carpten JD, Farnebo LO, Larsson C, Arnold A. Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. N Engl J Med 2003; 349: 1722 – 1729
[31] Howell VM, Haven CJ, Kahnoski K, Khoo SK, Petillo D, Chen J, Fleuren GJ, Robinson BG, Delbridge LW, Philips J, Nelson AE, Krause U, Hammje K, Dralle H, Hoang-Vu C, Gimm O, Marsh DJ, Morreau H, Teh BT. HRPT2 mutations are associated with malignancy in sporadic parathyroid tumours. J Med Genet 2003; 40: 657 – 663
[32] Haven CJ, Howell VM, Eilers PH, Dunne R, Takahashi M, van Puijenbroek M, Furge K, Kievit J, Tan MH, Fleuren GJ, Robinson BG, Delbridge LW, Philips J, Nelson AE, Krause U, Dralle H, Hoang-Vu C, Gimm O, Morreau H, Marsh DJ, Teh BT. Gene expression of parathyroid tumors: molecular subclassification and identification of the potential malignant phenotype. Cancer Res 2004; 64: 7405 – 7411
[33] Bertherat J, Gimenez-Roqueplo A-P. New insights in the genetics of adrenocortical tumors, pheochromocytomas, and paragangliomas. Horm Metab Res 2005; 37: 384 – 390
[34] Bertherat J, Groussin L, Sandrini F, Matyakhina L, Bei T, Stergiopoulos S, Papageorgiou T, Bourdeau I, Kirschner LS, Vincent-Dejean C, Perlemoine K, Gicquel C, Bertagna X, Stratakis CA. Molecular and functional analysis of PRKAR1A and its locus (17q22 – 24) in sporadic adrenocortical tumors: 17q losses, somatic mutations, and protein kinase A expression and activity. Cancer Res 2003; 63: 5308 – 5319
[35] Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Altehoefer C, Zerres K, Januszewicz A, Eng C, Smith WM, Munk R, Manz T, Glaesker S, Apel TW, Treier M, Reineke M, Walz MK, Hoang-Vu C, Brauckhoff M, Klein-Franke A, Klose P, Schmidt H, Maier-Woelfle M, Peczkowska M, Szmigielski C, Eng C. Freiburg-Warsaw-Columbus Pheochromocytoma Study Group. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med 2002; 346: 1459 – 1466
[36] Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, Muresan M, Buchta M, Franke G, Klisch J, Bley TA, Hoegerle S, Boedeker CC, Opocher G, Schipper J, Januszewicz A, Eng C. European-American Paraganglioma Study Group. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA 2004 Aug 25; 292: 943 – 951
[37] Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002; 108: 132 – 139
[38] Wolf A, Willenberg HS, Cupisti K, Schott M, Geddert H, Raffel A, Bornstein SR, Scherbaum WA, Knoefel WT. Adrenal pheochromocytoma with contralateral cortisol-producing adrenal adenoma: diagnostic and therapeutic management. Horm Metab Res 2005; 37: 391 – 395
[39] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57 – 70
[40] Khan J, Wei JS, Ringner M, Saal LH, Ladanyi M, Westermann F, Berthold F, Schwab M, Antonescu CR, Peterson C, Meltzer PS. Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks. Nat Med 2001; 7: 673 – 679
[41] Carlomagno F, Santoro M. Identification of RET kinase inhibitors as potential new treatment for sporadic and inherited thyroid cancer. J Chemother 2004; 16: 49 – 51